Impact of body weight on virological and immunological responses to efavirenz-containing regimens in HIV-infected, treatment-naive adults

Marzolini, Catia ; Sabin, Caroline ; Raffi, François ; Siccardi, Marco ; Mussini, Cristina ; Launay, Odile ; Burger, David ; Roca, Bernardino ; Fehr, Jan ; Bonora, Stefano ; Mocroft, Amanda ; Obel, Niels ; Dauchy, Frederic-Antoine ; Zangerle, Robert ; Gogos, Charalambos ; Gianotti, Nicola ; Ammassari, Adriana ; Torti, Carlo ; Ghosn, Jade ; Chêne, Genevieve ; Grarup, Jesper ; Battegay, Manuel

Abstract: OBJECTIVE: The prevalence of overweight and obesity is increasing among HIV-infected patients. Whether standard antiretroviral drug dosage is adequate in heavy individuals remains unresolved. We assessed the virological and immunological responses to initial efavirenz (EFV)-containing regimens in heavy compared to normal-weight HIV-infected patients. DESIGN: Observational European cohort collaboration study. METHODS: Eligible patients were antiretroviral-naïve with documented weight prior to EFV start and follow-up viral loads after treatment initiation. Cox regression analyses evaluated the association between weight and time to first undetectable viral load (<50 copies/ml) after treatment initiation, and time to viral load rebound (two consecutive viral load >50 copies/ml) after initial suppression over 5 years of follow-up. Recovery of CD4 cell count was evaluated 6 and 12 months after EFV initiation. Analyses were stratified by weight (kg) group (I - <55; II - >55, <80 (reference); III - >80, <85; IV - >85, <90; V - >90, <95; VI - >95). RESULTS: The study included 19 968 patients, of whom 9.1, 68.3, 9.1, 5.8, 3.5, and 4.3% were in weight groups I-VI, respectively. Overall, 81.1% patients attained virological suppression, of whom 34.1% subsequently experienced viral load rebound. After multiple adjustments, no statistical difference was observed in time to undetectable viral load and virological rebound for heavier individuals compared to their normal-weight counterparts. Although heaviest individuals had significantly higher CD4 cell count at baseline, CD4 cell recovery at 6 and 12 months after EFV initiation was comparable to normal-weight individuals. CONCLUSION: Virological and immunological responses to initial EFV-containing regimens were not impaired in heavy individuals, suggesting that the standard 600 mg EFV dosage is appropriate across a wide weight range.

DOI: https://doi.org/10.1097/QAD.0000000000000530

on virological and immunological responses to efavirenz-containing regimens in HIV-infected, treatment-naive adults. AIDS, 29(2):193-200.
DOI: https://doi.org/10.1097/QAD.0000000000000530

Impact of body weight on virological and immunological responses to efavirenz-containing regimens in HIV-infected, treatment-naive adults

Catia Marzolini[a,*], Caroline Sabin[b,*], François Raffi[c], Marco Siccardi[d], Cristina Mussini[e], Odile Launay[f], David Burger[g], Bernardino Roca[h], Jan Fehr[i], Stefano Bonora[j], Amanda Mocroft[b], Niels Obel[k], Frederic-Antoine Dauchy[l], Robert Zangerle[m], Charalambos Gogos[n], Nicola Gianotti[o], Adriana Ammassari[p], Carlo Torti[q], Jade Ghosn[r], Genevieve Chêne[s], Jesper Grarup[t], Manuel Battegay[a], for the Efavirenz, Obesity Project Team on behalf of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord

Objective: The prevalence of overweight and obesity is increasing among HIV-infected patients. Whether standard antiretroviral drug dosage is adequate in heavy individuals remains unresolved. We assessed the virological and immunological responses to initial efavirenz (EFV)-containing regimens in heavy compared to normal-weight HIV-infected patients.

Design: Observational European cohort collaboration study.

[a]Division of Infectious Diseases and Hospital Epidemiology, Departments of Medicine and Clinical Research, University Hospital of Basel, Basel, Switzerland, [b]Department of Infection and Population Health, University College London, London, UK, [c]Division of Infectious Diseases, University Hospital of Nantes, Nantes, France, [d]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK, [e]Clinic of Infectious Diseases, University of Modena, Modena, Italy, [f]University Paris Descartes, Paris, France, [g]Radboud University Medical Centre, Nijmegen, the Netherlands, [h]Hospital General of Castellon, University of Valencia and University Jaume I, Valencia, Spain, [i]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich and University of Zurich, Zurich, Switzerland, [j]Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy, [k]Department of Infectious Diseases, Copenhagen University Hospital, Copenhagen, Denmark, [l]Department of Infectious and Tropical Diseases, HIV Unit, University Hospital Pellegrin, Bordeaux, France, [m]Medical University Innsbruck, Innsbruck, Austria, [n]Department of Internal Medicine, University Hospital of Patras, Patras, Greece, [o]Department of Infectious Diseases, San Raffaele Scientific Institute, Milan, [p]Clinical Department, National Institute for Infectious Diseases 'L. Spallanzani', Rome, [q]Division of Infectious and Tropical Diseases, University and Ospedali Civili of Brescia, Brescia, Italy, [r]Paris Descartes University, EA 7327, Necker School of Medicine, Paris and APHP, UF de Thérapeutique en Immuno-Infectiologie, Hôpital de l'Hôtel-Dieu, Paris, [s]University of Bordeaux, ISPED, Centre INSERM U897-Epidémiologie Statistique, Bordeaux, France, and [t]Copenhagen HIV Programme, University of Copenhagen, Copenhagen, Denmark.

Correspondence to Catia Marzolini, PhD, Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Basel, Petersgraben 4, CH-4031 Basel, Switzerland.

Tel: +41 61 265 47 46; fax: +41 61 265 31 98; e-mail: Catia.Marzolini@usb.ch

[*] Catia Marzolini and Caroline Sabin contributed equally to this work.

Received: 3 September 2014; revised: 16 October 2014; accepted: 28 October 2014.

DOI:10.1097/QAD.0000000000000530

Methods: Eligible patients were antiretroviral-naïve with documented weight prior to EFV start and follow-up viral loads after treatment initiation. Cox regression analyses evaluated the association between weight and time to first undetectable viral load (<50 copies/ml) after treatment initiation, and time to viral load rebound (two consecutive viral load >50 copies/ml) after initial suppression over 5 years of follow-up. Recovery of $CD4^+$ cell count was evaluated 6 and 12 months after EFV initiation. Analyses were stratified by weight (kg) group (I – <55; II – >55, <80 (reference); III – >80, <85; IV – >85, <90; V – >90, <95; VI – >95).

Results: The study included 19 968 patients, of whom 9.1, 68.3, 9.1, 5.8, 3.5, and 4.3% were in weight groups I–VI, respectively. Overall, 81.1% patients attained virological suppression, of whom 34.1% subsequently experienced viral load rebound. After multiple adjustments, no statistical difference was observed in time to undetectable viral load and virological rebound for heavier individuals compared to their normal-weight counterparts. Although heaviest individuals had significantly higher $CD4^+$ cell count at baseline, $CD4^+$ cell recovery at 6 and 12 months after EFV initiation was comparable to normal-weight individuals.

Conclusion: Virological and immunological responses to initial EFV-containing regimens were not impaired in heavy individuals, suggesting that the standard 600 mg EFV dosage is appropriate across a wide weight range.

Video Abstract: http://links.lww.com/QAD/A635

AIDS 2015, **29**:193–200

Keywords: efavirenz, HIV, immunological response, virological response, weight

Introduction

Whereas the use of effective combination antiretroviral therapies (cARTs) has considerably reduced the prevalence of HIV-associated wasting, the prevalence of overweight and obesity has increased among HIV-infected individuals partly due to improved health [1–6]. Obesity can alter the pharmacokinetics of drugs [7]. Consequently, standard drug doses may be insufficient in heavy individuals. Suboptimal treatment response has indeed been reported in a morbidly obese HIV-infected patient treated with the standard 600 mg efavirenz (EFV) dose [8]. Furthermore, EFV levels were shown to be inversely correlated to body weight [9,10].

Obesity is also characterized by a chronic state of inflammation with the release of pro-inflammatory or immune-modulating factors [11]. The impact of overweight and obesity on the immune response in HIV infection remains unclear. Studies from the pre-cART era found that overweight and obesity were associated with a slower disease progression [12–14]. Conversely, in a more recent study, overweight and obesity have been associated with lower $CD4^+$ recovery after cART initiation [15], although this had not been consistently reported [16,17].

There are currently no comparisons of the virological and immunological responses to initial EFV-containing regimens in HIV-infected individuals across a wide range of body weights. We hypothesized that heavy individuals may be underdosed and, consequently, may have a less vigorous virological response or be at risk for virological failure or may have an inferior immune response to treatment compared to normal-weight patients.

Methods

Study population

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) includes 33 HIV cohorts within the EuroCoord network (www.EuroCoord.net) [18].

All HIV-infected adults enrolled in COHERE and starting an EFV-containing regimen were considered for inclusion. Patients were excluded if their weight was missing or if they did not have at least one viral load measurement before and after EFV initiation. To limit confounding, the analysis was limited to cART-naive individuals.

Definitions

Weight, rather than BMI, was considered, as height was not provided routinely by all cohorts. Analyses were performed by stratifying weight into six groups defined as: I (underweight) – below 55 kg; II (normal weight) – at least 55, below 80 kg; III – at least 80, below 85 kg; IV – at least 85, below 90 kg; V – at least 90, below 95 kg; and VI – at least 95 kg. Baseline weight, $CD4^+$ cell count,

and viral load were selected as the most recent values prior to EFV initiation.

Statistical methods

Kaplan–Meier plots were used to describe the time to initial viral suppression after treatment initiation and the time to subsequent virological rebound. Initial viral suppression was defined as the first viral load 50 copies/ml or less, and virological rebound was defined as the first two consecutive viral load above 50 copies/ml. For our primary analyses of virological rebound, treatment switches were ignored. However, several sensitivity analyses considered variations to this definition (see below). Cox proportional-hazard regression analyses were used to compare weight groups before and after adjustment for sex, age, mode of HIV acquisition, ethnicity, hepatitis/abnormal liver function test, pretreatment $CD4^+$ cell count and viral load, prior AIDS, nucleoside reverse transcriptase inhibitor (NRTI) backbone, protease inhibitor co-administration, cohort and calendar year.

Sensitivity analyses were performed to investigate the robustness of the results to the way in which the virological rebound endpoint was defined. In particular, analyses were repeated after censoring each individual's follow-up on the date of EFV discontinuation, if this occurred prior to virological rebound; the primary analysis was repeated after including into the definition of virological rebound individuals with one viral load above 50 copies/ml, who then changed their cART regimen and discontinued EFV; the virological rebound definition was modified to require two viral loads above 400 copies/ml or 1000 copies/ml; and virological rebound was defined as one viral load above 50 copies/ml.

Furthermore, analyses were performed after stratifying by sex and ethnicity, with tests of interaction performed to assess whether there were significant differences in the associations between sex, white/non-white ethnicity, and the weight groups.

The change in absolute $CD4^+$ cell count during follow-up was calculated as the difference between the $CD4^+$ values measured 6 and 12 months after EFV start and the baseline value. The impact of weight on the $CD4^+$ cell count change 6 and 12 months after EFV start was analyzed using multiple linear regression analyses adjusted as described above. Statistical analyses were performed using SAS version 9.13 (Cary, North Carolina, USA).

Results

Patient characteristics

In total, 19 968 individuals from 12 different cohorts were included. The demographic and clinical characteristics of the study population differed by weight categories as described in Table 1. When looking at the weight distribution in different calendar periods, the proportion of heavier individuals was greater in more recent years (Table 1, Supplementary Fig. 1, http://links.lww.com/QAD/A625).

Virological response

Overall, 16 188 (81.1%) individuals achieved an undetectable viral load after starting EFV. Adjusted Cox regression analyses for the time to initial undetectable viral load showed that underweight individuals were less likely to attain an undetectable viral load relative to normal-weight individuals [relative hazard 0.91; 95% confidence interval (CI) 0.86, 0.97; $P = 0.004$], whereas no statistical difference was observed between heavier and normal-weight groups (Table 2a, Supplementary Fig. 2a, http://links.lww.com/QAD/A625).

Of the 16 188 patients attaining an undetectable viral load, 5525 (34.1%) subsequently experienced viral load rebound. Cumulative probability of virological rebound was significantly higher for underweight compared to normal-weight individuals ($P = 0.0001$, log-rank test) (Supplementary Fig. 2b, http://links.lww.com/QAD/A625). However, no significant differences were observed among weight categories for the time to viral rebound in adjusted Cox analyses (Table 2b). The results remained consistent when repeating the analyses after censoring at the time of EFV discontinuation or when using different thresholds for viral rebound. Furthermore, no substantial differences were seen in the associations between weight group and either the time to initial viral suppression or subsequent viral rebound when stratifying by sex or ethnicity (all interaction P values >0.05).

Immunological response

The absolute $CD4^+$ values 6 and 12 months after therapy initiation were significantly higher with increasing weight categories (Table 2c). In adjusted multivariable linear regression analyses, the difference in absolute $CD4^+$ cell counts remained significant for the heaviest individuals both at 6 [beta estimate 14.4, standard error (SE) 7.1, $P = 0.04$] and 12 (beta estimate 17.2, SE 8.6, $P = 0.05$) months (Table 2d). However, the $CD4^+$ cell recovery was comparable between heavier and normal-weight individuals.

Discussion

Overall, 22.7% of our study population fell in the heavyweight categories. The proportion of heavier individuals tended to be greater in more recent years. Also, heavier individuals were older, less likely to have acquired HIV infection via intravenous drug user (IDU) or to have AIDS prior to EFV start, more likely to have higher baseline $CD4^+$ values or to be treated with tenofovir + emtricitabine. Collectively, these observations may reflect calendar trends towards an earlier diagnosis and

Table 1. Characteristics of patients at the start of efavirenz, overall, and stratified by weight group.

Characteristics	All patients	Weight (kg)						
		<55	>55, <80	>80, <85	>85, <90	>90, <95	>95	*P*
Number of patients	19968 (100.0)	1811 (9.1)	13628 (68.3)	1823 (9.1)	1148 (5.8)	704 (3.5)	854 (4.3)	
Age (years) median (IQR)	38 (32, 45)	35 (29, 43)	38 (31, 45)	40 (34, 47)	40 (34, 47)	40 (34, 47)	42 (36, 49)	0.0001
Female sex	4495 (22.5)	1146 (63.3)	2840 (20.8)	197 (10.8)	117 (10.2)	79 (11.2)	116 (13.6)	0.0001
Ethnicity								
White	5729 (28.7)	515 (28.4)	3931 (28.9)	514 (28.2)	336 (29.3)	204 (29.0)	229 (26.8)	0.0001
Black	487 (2.4)	72 (4.0)	321 (2.4)	36 (2.0)	29 (2.5)	12 (1.7)	17 (2.0)	
Other	180 (0.9)	45 (2.5)	110 (0.8)	14 (0.8)	8 (0.7)	2 (0.3)	1 (0.1)	
Prohibited	13007 (65.1)	1107 (61.1)	8888 (65.2)	1213 (66.5)	751 (65.4)	465 (66.1)	583 (68.3)	
Not known	565 (2.8)	72 (4.0)	378 (2.8)	46 (2.5)	24 (2.1)	21 (3.0)	24 (2.8)	
Mode of HIV infection								
MSM	9046 (45.3)	316 (17.5)	6469 (47.5)	946 (51.9)	592 (51.6)	326 (46.3)	397 (46.5)	0.0001
IDU	1593 (8.0)	239 (13.2)	1130 (8.3)	95 (5.2)	54 (4.7)	43 (6.1)	32 (3.8)	
Heterosexual	7885 (39.5)	1070 (59.1)	5110 (37.5)	638 (35.0)	423 (36.9)	274 (38.9)	370 (43.3)	
Other	317 (1.6)	60 (3.3)	185 (1.4)	25 (1.4)	19 (1.7)	12 (1.7)	16 (1.9)	
Not known	1127 (5.6)	126 (7.0)	734 (5.4)	119 (6.5)	60 (5.2)	49 (7.0)	39 (4.6)	
AIDS prior to EFV	3065 (15.4)	537 (29.7)	2107 (15.5)	183 (10.0)	109 (9.5)	69 (9.8)	60 (7.0)	0.0001
$CD4^+$ cell count (cells/μl)								
Median (IQR)	221 (50, 325)	169 (36, 288)	223 (53, 328)	235 (60, 339)	235 (31, 330)	236 (32, 322)	241 (40, 330)	0.0001
Viral load (log_{10} copies/ml)								
Median (IQR)	4.8 (4.3, 5.3)	4.9 (4.4, 5.4)	4.8 (4.3, 5.3)	4.8 (4.3, 5.2)	4.8 (4.3, 5.2)	4.8 (4.3, 5.2)	4.7 (4.2, 5.2)	0.0001
Year of EFV start								
<2000	1816 (9.1)	252 (13.9)	1285 (9.4)	135 (7.4)	65 (5.7)	39 (5.5)	40 (4.7)	0.0001
2001/2002	1909 (9.6)	250 (13.8)	1328 (9.7)	145 (8.0)	70 (6.1)	56 (8.0)	60 (7.0)	
2003/2004	2479 (12.4)	307 (17.0)	1711 (12.6)	204 (11.2)	105 (9.2)	61 (8.7)	91 (10.7)	
2005/2006	3056 (15.3)	306 (16.9)	2112 (15.5)	249 (13.7)	171 (14.9)	94 (13.4)	124 (14.5)	
2007/2008	4015 (20.1)	302 (16.7)	2700 (19.8)	359 (19.7)	273 (23.8)	190 (27.0)	191 (22.4)	
2009/2010	4414 (22.1)	261 (14.4)	2972 (21.8)	477 (26.2)	307 (26.7)	168 (23.9)	229 (26.8)	
2011/2012/2013	2279 (11.4)	133 (7.3)	1520 (11.2)	254 (13.9)	157 (13.7)	96 (13.6)	119 (13.9)	
NRTI backbone								
None	51 (0.3)	6 (0.3)	27 (0.2)	8 (0.4)	5 (0.4)	3 (0.4)	2 (0.2)	0.0001
TDF+FTC	10881 (54.5)	719 (39.7)	7366 (54.1)	1089 (59.7)	719 (62.6)	444 (63.1)	544 (63.7)	
ZDV+3TC	3904 (19.6)	450 (24.9)	2703 (19.8)	334 (18.3)	178 (15.5)	106 (15.1)	133 (15.6)	
Other combination	5132 (25.7)	636 (35.1)	3532 (25.9)	392 (21.5)	246 (21.4)	151 (21.4)	20 (2.3)	
On a PI	643 (3.2)	69 (3.8)	430 (3.2)	57 (3.1)	47 (4.1)	20 (2.8)	20 (2.3)	0.19
Abnormal LFT	772 (3.9)	82 (4.5)	496 (3.6)	69 (3.8)	53 (4.6)	29 (4.1)	43 (5.0)	0.11
HCV positive or HBV positive	2670 (13.4)	304 (16.8)	1894 (13.9)	203 (11.1)	113 (9.8)	76 (10.8)	80 (9.4)	0.0001

Entries are *n* (%) unless otherwise stated. 3TC, lamivudine; EFV, efavirenz; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, intravenous drug user; IQR, interquatile range; LTF, liver function test; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir; ZDV, zidovudine.

Table 2. Virological and immunological responses.

(a)

Weight (kg)	Median (months)	Unadjusted		Adjusted	
		RH (95% CI)	*P*	RH (95% CI)	*P*
<55	4.8	0.90 (0.85, 0.95)	0.0002	0.91 (0.86, 0.97)	0.004
>55, <80	4.5	1	–	1	–
>80, <85	4.2	1.07 (1.01, 1.13)	0.02	1.05 (0.99, 1.11)	0.13
>85, <90	4.5	1.06 (0.99, 1.13)	0.09	1.00 (0.93, 1.07)	0.96
>90, <95	4.6	1.03 (0.95, 1.12)	0.51	0.98 (0.90, 1.07)	0.69
>95	4.2	1.10 (1.02, 1.19)	0.01	1.07 (0.99, 1.16)	0.09

(b)

Weight (kg)	Unadjusted		Adjusted	
	RH (95% CI)	*P*	RH (95% CI)	*P*
<55	1.25 (1.15, 1.36)	0.0001	0.99 (0.90, 1.09)	0.78
>55, <80	1	–	1	–
>80, <85	0.86 (0.78, 0.95)	0.003	0.96 (0.86, 1.06)	0.38
>85, <90	0.81 (0.72, 0.92)	0.0008	0.99 (0.87, 1.13)	0.91
>90, <95	0.89 (0.77, 1.03)	0.13	1.06 (0.91, 1.24)	0.45
>95	0.86 (0.75, 0.99)	0.03	1.02 (0.88, 1.17)	0.84

(c)

Weight (kg)	6 months		12 months	
	Absolute value Median (IQR)	Increase from baseline Median (IQR)	Absolute value Median (IQR)	Increase from baseline Median (IQR)
<55	262 (124, 426)	99 (19, 190)	317 (166, 481)	139 (43, 239)
>55, <80	323 (134, 473)	88 (10, 179)	357 (163, 523)	120 (14, 233)
>80, <85	333 (115, 482)	80 (9, 180)	365 (154, 529)	104 (11, 230)
>85, <90	332 (73, 482)	87 (9, 181)	378 (103, 539)	120 (12, 231)
>90, <95	335 (47, 476)	70 (8, 173)	380 (87, 534)	111 (10, 230)
>95	340 (70, 485)	83 (8, 183)	390 (180, 520)	123 (17, 245)
P (Mann–Whitney)	0.0001	0.03	0.02	0.009
Overall	321 (129, 471) *N* = 12 779	88 (10, 180) *N* = 12 232	357 (160, 520) *N* = 11 072	121 (14, 234) *N* = 10 572

(d)

Weight (kg)	6 months		12 months	
	Beta (SE)	*P*	Beta (SE)	*P*
<55	9.4 (5.3)	0.08	4.8 (6.6)	0.47
>55, <80	0	–	0	–
>80, <85	5.9 (5.1)	0.25	1.8 (6.2)	0.76
>85, <90	7.4 (6.2)	0.23	12.0 (7.6)	0.11
>90, <95	−5.3 (7.7)	0.49	3.1 (9.6)	0.74
>95	14.4 (7.1)	0.04	17.2 (8.6)	0.05

Cox proportional-hazard regression analyses of associations between weight and the time to an initial undetectable viral load after treatment initiation (a), and the time to subsequent viral load rebound after initial virological suppression (b), absolute $CD4^+$ cell counts 6 and 12 months after efavirenz initiation (c) and beta estimates from adjusted multivariable linear regression analyses of factors associated with the absolute $CD4^+$ cell counts 6 and 12 months after efavirenz initiation. CI, confidence interval; IQR, interquartile range; *N*, total number; RH, relative hazard; SE, standard error. Analyses were adjusted for demographic factors (sex, age, ethnicity); mode of HIV infection; cohort and calendar year; any hepatitis or any abnormal liver function test; viral load; baseline $CD4^+$ cell count; prior AIDS; and NRTI backbone and concomitant receipt of PI.

treatment with effective drugs [19,20]. Changes in demographics may also be responsible for the observed changes in weight distribution over the years. Consistent with our observations, a recent analysis of the Swiss HIV Cohort Study showed that increasing overweight and obesity rates were explained by the aging of the HIV population, fewer IDU, earlier treatment initiation, and better cART coverage over the years [4].

We showed no difference in the virological response to EFV-based therapy between heavy and normal-weight individuals. Of note, the ability to detect differences may

have been limited by the small number of patients weighting above 120 kg. EFV 900 mg once daily (q.d.) has been shown to produce a similar exposure in individuals weighting 100–120 kg than the exposure obtained with the standard EFV 600 mg q.d. dosage in normal-weight individuals [8]. Interestingly, EFV given at 400 mg q.d. has been shown to be noninferior to the standard dose when combined with tenofovir and emtricitabine in treatment-naïve patients [21]. Thus, one could speculate that the standard EFV dose has an efficacy margin which is sufficient for a certain degree of obesity. This efficacy margin may also result from the use of more potent NRTI backbone in recent years [22]. In our study, underweight individuals had a significantly longer time to initial viral suppression compared to normal-weight individuals. Of note, the proportion of individuals infected through IDU and with AIDS prior to EFV initiation was higher in the underweight category; thus the longer time to initial suppression might be a consequence of poorer adherence, later presentation, or more advanced disease possibly resulting in drug malabsorption. However, there was no difference in the time to viral rebound between these weight categories after adjustment.

Obesity has been associated with the release of factors which may impact the immune function [11]. Leptin has notably been shown to promote T-cell proliferation and activation *in vitro* [23,24]. Thus, heavy individuals might have a different pattern of immune reconstitution. We showed that heavier individuals had higher $CD4^+$ cell counts at baseline and after initiating EFV, whereas the pattern of $CD4^+$ recovery was comparable to normal-weight individuals and within expected ranges [25]. The observed higher baseline $CD4^+$ values may reflect calendar trends towards earlier diagnosis and treatment, but could also be related to leptin-associated T-cell proliferation. An increase in $CD4^+$ cell counts has indeed been described both in obese HIV-uninfected [26,27] and HIV-infected populations [17,28]. Underweight individuals had lower baseline $CD4^+$ values, but a higher recovery compared to normal-weight individuals. Lower $CD4^+$ values at baseline could result from the underlying malnutrition or a more advanced disease, whereas younger age and higher nadir $CD4^+$ cell count might explain the higher recovery [29].

Despite previous reports of sex differences in EFV exposure [30,31] and in leptin level [32,33], which was shown to be inversely correlated to HIV replication [34], our study did not find any sex difference in the association with weight. Of note, the ability to detect a difference may have been limited by the small number of women. In addition, despite known ethnicity-related genetic differences in EFV metabolism [35], we did not find any evidence that the association with weight differed by ethnicity. Again, this could possibly result from the small proportion of individuals of known black ethnicity.

Strengths of this study include the large size and the broad geographical representation. However, this observational study has limitations. Most cohorts do not measure levels of EFV; therefore we could not correlate our observations to drug concentrations. Data on EFV dosage were not available; thus potential adjustments cannot be excluded. The effect of adherence on treatment response could not be assessed, although adherence patterns are not expected to differ between heavy and normal-weight categories. The number of individuals with extreme weights was low, limiting any conclusions that could be drawn for severely obese patients.

In conclusion, in this large European collaborative study, virological and immunological responses to initial EFV-containing regimens given at the standard 600 mg dose were not impaired in heavy treatment-naive individuals, suggesting that the standard dosage is appropriate across a wide weight range. However, due to the limited number of individuals weighting above 120 kg, response to EFV should be monitored carefully in severely obese individuals.

Acknowledgements

The Efavirenz and Obesity Project Working Team included Catia Marzolini, Caroline Sabin, François Raffi, Marco Siccardi, Cristina Mussini, Odile Launay, David Burger, Bernardino Roca, Jan Fehr, Stefano Bonora, Amanda Mocroft, Niels Obel, Frederic-Antoine Dauchy, Robert Zangerle, Charalambos Gogos, Nicola Gianotti, Adriana Ammassari, Carlo Torti, Jade Ghosn, Genevieve Chêne, Jesper Grarup, and Manuel Battegay.

Members of the collaboration of Observational HIV Epidemiological Research Europe (COHERE) group: COHERE Steering Committee – Contributing Cohorts: Robert Zangerle (AHIVCOS), Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11 OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE, and ANRS CO13 HEPAVIH), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Peter Reiss (ATHENA), Ferdinand Wit (ATHENA), Maria Prins (CASCADE), Heiner Bucher (CASCADE), Caroline Sabin (CHIC), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne-Bonn), Julia Del Amo (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Perez-Hoyos (GEMES-Haemo), Osamah Hamouda (German ClinSurv), Barbara Bartmeyer (German ClinSurv), Nikoloz Chkhartishvili (Georgian National HIV/AIDS), Antoni Noguera-Julian (CORISPE-cat), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA), Norbert Brockmeyer

(KOMPNET), Luis Prieto (Madrid PMTCT Cohort), Pablo Rojo Conejo (CORISPES-Madrid), Antoni Soriano-Arandes (NENEXP), Manuel Battegay (SHCS), Andri Rauch (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miro (PISCIS), Antonella Castagna (San Raffaele), Deborah Konopnick (St. Pierre Cohort), Tessa Goetghebuer (St Pierre Pediatric Cohort), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH), David Haerry (European AIDS Treatment Group).

COHERE Executive Committee: Stéphane de Wit (Chair, St Pierre University Hospital), Jordi Casabona (PISCIS), Dominique Costagliola (FHDH), Antonella d'Arminio-Monforte (ICONA), Manuel Battegay (SHCS), Julia del Amo (CoRIS), Amanda Mocroft (EuroSida), Dorthe Raben (Head, Copenhagen Regional Coordinating Centre), Genevieve Chêne (Head, Bordeaux Regional Coordinating Centre). Paediatric Cohort Representatives: Ali Judd, Pablo Rojo Conejo.

COHERE Regional Coordinating Centres: Bordeaux RCC: Diana Barger, Céline Colin, Christine Schwimmer, Monique Termote, Linda Wittkop; Copenhagen RCC: Maria Campbell, Nina Friis-Moller, Jesper Kjaer, Dorthe Raben, Rikke Salbol Brandt.

Project Leaders and Statisticians: Manuel Battegay, Julia Bohlius, Vincent Bouteloup, Heiner Bucher, Alessandro Cozzi-Lepri, François Dabis, Antonella d'Arminio Monforte, Julia del Amo, Maria Dorrucci, Matthias Egger, Hansjakob Furrer, Ali Judd, Ole Kirk, Olivier Lambotte, Sara Lodi, Sophie Matheron, Laurence Meyer, Jose Miro, Amanda Mocroft, Susana Monge, Fumiyo Nakagawa, Roger Paredes, Andrew Phillips, Massimo Puoti, Caroline Sabin, Colette Smit, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, Giota Touloumi, Marc van der Valk, Linda Wittkop, Natasha Wyss.

The COHERE acknowledgement appendix may be found at: http://www.chip.dk/COHERE/Acknowledgements/tabid/320/Default.aspx

The COHERE study group has received unrestricted funding from: Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, The Netherlands; and the Augustinus Foundation, Denmark. COHERE receives funding from the European Union Seventh Framework Programme (FP7/2007–2013) under EuroCoord grant agreement n°260694. A list of the founders of the participating cohorts can be found at http://www.cohere.org.

The study sponsors had no role in the design of the study, the collection, analysis and interpretation of data, the writing of the report or the decision to submit the paper for publication.

Conflicts of interest

C.M. is a recipient of a grant for the clinical research from the University of Basel (grant DMS2265).

No member of the working team for this report has any financial relationship with organizations that could influence this work, although most members of the group have received in the past funding for research, travel grants, consultancy fees or speaking engagements as detailed below.

Support for travel to meetings for the study or other purposes: G.C. (Eu FP7 EuroCoord).

Grants/grants pending: C.Ma. (University of Basel), M.B. (Abbvie, BMS, Boehringer-Ingelheim, Gilead, Janssen, MSD, Pfizer, ViiV), G.C. (Eu FP7 EuroCoord), J.F. (Abbvie, BMS, Gilead, Janssen, MSD, ViiV), J.Gh. (Merck), N.G. (Janssen, Gilead, ViiV), J.Gr. (EuroCoord), A.M. (see funding acknowledgements), C.Mu. (COHERE), N.O. (BMS, Glaxo, Boehringer-Ingelheim, Gilead), C.S. (Eu FP7), C.T. (Gilead), Robert Zangerle (Gilead).

Board membership: A.A. (MSD), M.B. (Gilead, MSD, Pfizer, ViiV), S.B. (ViiV, Merck, Gilead, Janssen, Abbvie), J.F. (Federal Commission for Sexual Health), J.Gh. (Merck, BMS, Gilead), N.G. (Janssen, Gilead, Abbvie), C.Mu. (BMS, MSD, ViiV, Gilead, Abbvie, Janssen), F.R. (Gilead, Janssen, Merck, MSD, ViiV), C.S. (Gilead, ViiV, Janssen, BMS), M.S. (Janssen, ViiV, Simcyp), C.T. (Gilead, ViiV).

Consultancy: J.F. (BMS, Gilead, Janssen, MSD, ViiV), C.G. (Pfizer, Gilead), F.R. (Gilead, Janssen, Merck, ViiV).

Payment for lectures including service on speakers bureaus: S.B. (ViiV, Gilead, Merck, BMS, Janssen, Abbvie), G.C. (Gilead, Tibotec-Janssen, Roche, MSD, Boehringer-Ingelheim, BMS, Glaxo, ViiV, Mylan, Abbvie, Pfizer for ANRS trials and for IWHOD), C.G. (BMS, Pfizer, Gilead), C.Mu. (BMS, MSD, ViiV, Gilead, Abbvie, Janssen), F.R. (Gilead, Janssen, Merck, ViiV), C.S. (Gilead, BMS, Abbvie, Janssen, ViiV), C.T. (Gilead, ViiV, Roche).

Travel, accomodations, teaching expenses unrelated to activities listed: G.C., J.F. (Abbvie, BMS, Gilead, Janssen, MSD, ViiV), J.Gh. (Merck, BMS, Gilead, ViiV), F.R. (ViiV), C.S. (BMS), N.G. (Janssen, Gilead), R.Z. (GSK, Janssen).

Payment for development of educational presentations: F.R. (Abbvie, Merck), C.S. (Gilead, BMS, ViiV, Janssen).

References

1. Amorosa V, Synnestvedt M, Gross R, Friedman H, MacGregor RR, Gudonis D, *et al*. **A tale of 2 epidemics: the intersection between obesity and HIV infection in Philadelphia.** *J Acquir Immune Defic Syndr* 2005; **39**:557–561.
2. Crum-Cianflone N, Roediger MP, Eberly L, Headd M, Marconi V, Ganesan A, *et al*. **Increasing rates of obesity among HIV-infected persons during the HIV epidemic.** *PLoS One* 2010; **5**:e10106.
3. Crum-Cianflone N, Tejidor R, Medina S, Barahona I, Ganesan A. **Obesity among patients with HIV: the latest epidemic.** *AIDS Patient Care STDS* 2008; **22**:925–930.
4. Hasse B, Iff M, Ledergerber B, Calmy A, Schmid P, Hauser C, *et al*. **Obesity trends and body mass index changes after starting antiretroviral treatment: the Swiss HIV Cohort Study.** *Open Forum Inf Dis* 2014; **1**:.
5. Lakey W, Yang LY, Yancy W, Chow SC, Hicks C. **Short communication: from wasting to obesity: initial antiretroviral therapy and weight gain in HIV-infected persons.** *AIDS Res Hum Retroviruses* 2013; **29**:435–440.
6. Tate T, Willig AL, Willig JH, Raper JL, Moneyham L, Kempf MC, *et al*. **HIV infection and obesity: where did all the wasting go?** *Antivir Ther* 2012; **17**:1281–1289.
7. Hanley MJ, Abernethy DR, Greenblatt DJ. **Effect of obesity on the pharmacokinetics of drugs in humans.** *Clin Pharmacokinet* 2010; **49**:71–87.
8. de Roche M, Siccardi M, Stoeckle M, Livio F, Back D, Battegay M, Marzolini C. **Efavirenz in an obese HIV-infected patient: a report and an in vitro-in vivo extrapolation model indicate risk of underdosing.** *Antivir Ther* 2012; **17**:1381–1384.
9. Poeta J, Linden R, Antunes MV, Real L, Menezes AM, Ribeiro JP, Sprinz E. **Plasma concentrations of efavirenz are associated with body weight in HIV-positive individuals.** *J Antimicrob Chemother* 2011; **66**:2601–2604.
10. Stohr W, Back D, Dunn D, Sabin C, Winston A, Gilson R, *et al*. **Factors influencing efavirenz and nevirapine plasma concentration: effect of ethnicity, weight and co-medication.** *Antivir Ther* 2008; **13**:675–685.
11. Koethe JR, Hulgan T, Niswender K. **Adipose tissue and immune function: a review of evidence relevant to HIV infection.** *J Infect Dis* 2013; **208**:1194–1201.
12. Jones CY, Hogan JW, Snyder B, Klein RS, Rompalo A, Schuman P, Carpenter CC. **Overweight and human immunodeficiency virus (HIV) progression in women: associations HIV disease progression and changes in body mass index in women in the HIV epidemiology research study cohort.** *Clin Infect Dis* 2003; **37 (Suppl 2)**:S69–S80.
13. Shor-Posner G, Campa A, Zhang G, Persaud N, Miguez-Burbano MJ, Quesada J, *et al*. **When obesity is desirable: a longitudinal study of the Miami HIV-1-infected drug abusers (MIDAS) cohort.** *J Acquir Immune Defic Syndr* 2000; **23**:81–88.
14. Shuter J, Chang CJ, Klein RS. **Prevalence and predictive value of overweight in an urban HIV care clinic.** *J Acquir Immune Defic Syndr* 2001; **26**:291–297.
15. Crum-Cianflone NF, Roediger M, Eberly LE, Vyas K, Landrum ML, Ganesan A, *et al*. **Obesity among HIV-infected persons: impact of weight on CD4 cell count.** *AIDS* 2010; **24**:1069–1072.
16. Tedaldi EM, Brooks JT, Weidle PJ, Richardson JT, Baker RK, Buchacz K, *et al*. **Increased body mass index does not alter response to initial highly active antiretroviral therapy in HIV-1-infected patients.** *J Acquir Immune Defic Syndr* 2006; **43**:35–41.
17. Koethe JR, Jenkins CA, Shepherd BE, Stinnette SE, Sterling TR. **An optimal body mass index range associated with improved immune reconstitution among HIV-infected adults initiating antiretroviral therapy.** *Clin Infect Dis* 2011; **53**:952–960.
18. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group. Bohlius J, Schmidlin K, Costagliola D, Fätkenheuer G, May M, Caro Murillo AM, *et al*. **Prognosis of HIV-associated non-Hodgkin lymphoma in patients starting combination antiretroviral therapy.** *AIDS* 2009; **23**:2029–2037.
19. Haines CF, Fleishman JA, Yehia BR, Berry SA, Moore RD, Bamford LP, Gebo KA. **Increase in CD4 count among new enrollees in HIV care in the modern antiretroviral therapy era.** *J Acquir Immune Defic Syndr* 2014; **67**:84–90.
20. Mocroft A, Lundgren JD, Sabin ML, Monforte AD, Brockmeyer N, Casabona J, *et al*. **Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE).** *PLoS Med* 2013; **10**: e1001510.
21. ENCORE1 Study Group, Puls R, Amin J, Losso M, Phanuphak P, Nwizu C, Orrell C, *et al*. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, noninferiority trial. Lancet 2014; 383: 1474–1482.
22. Sax PE, Tierney C, Collier AC, Fischl MA, Mollan K, Peeples L, *et al*. **Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy.** *N Engl J Med* 2009; **361**:2230–2240.
23. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. **Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression.** *Nature* 1998; **394**:897–901.
24. Martin-Romero C, Santos-Alvarez J, Goberna R, Sanchez-Margalet V. **Human leptin enhances activation and proliferation of human circulating T lymphocytes.** *Cell Immunol* 2000; **199**:15–24.
25. van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, *et al*. **Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study.** *Lancet* 2004; **363**:1253–1263.
26. Nieman DC, Henson DA, Nehlsen-Cannarella SL, Ekkens M, Utter AC, Butterworth DE, Fagoaga OR. **Influence of obesity on immune function.** *J Am Diet Assoc* 1999; **99**:294–299.
27. Womack J, Tien PC, Feldman J, Shin JH, Fennie K, Anastos K, *et al*. **Obesity and immune cell counts in women.** *Metabolism* 2007; **56**:998–1004.
28. Adeyemi OM, Vibhakar S, Evans AT. **Obesity and lymphocyte subsets in virologically suppressed HIV-infected patients.** *Metabolism* 2009; **58**:1285–1287.
29. Kaufmann GR, Bloch M, Finlayson R, Zaunders J, Smith D, Cooper DA. **The extent of HIV-1-related immunodeficiency and age predict the long-term CD4 T lymphocyte response to potent antiretroviral therapy.** *AIDS* 2002; **16**:359–367.
30. Barrett JS, Joshi AS, Chai M, Ludden TM, Fiske WD, Pieniaszek HJ Jr. **Population pharmacokinetic meta-analysis with efavirenz.** *Int J Clin Pharmacol Ther* 2002; **40**:507–519.
31. Burger D, van der Heiden I, la Porte C, van der Ende M, Groeneveld P, Richter C, *et al*. **Interpatient variability in the pharmacokinetics of the HIV nonnucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism.** *Br J Clin Pharmacol* 2006; **61**:148–154.
32. Couillard C, Mauriege P, Prud'homme D, Nadeau A, Tremblay A, Bouchard C, Després JP. **Plasma leptin concentrations: gender differences and associations with metabolic risk factors for cardiovascular disease.** *Diabetologia* 1997; **40**: 1178–1184.
33. Saad MF, Damani S, Gingerich RL, Riad-Gabriel MG, Khan A, Boyadjian R, *et al*. **Sexual dimorphism in plasma leptin concentration.** *J Clin Endocrinol Metab* 1997; **82**:579–584.
34. Azzoni L, Crowther NJ, Firnhaber C, Foulkes AS, Yin X, Glencross D, *et al*. **Association between HIV replication and serum leptin levels: an observational study of a cohort of HIV-1-infected South African women.** *J Int AIDS Soc* 2010; **13**:33.
35. Haas DW, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, *et al*. **Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study.** *AIDS* 2004; **18**:2391–2400.